Variant: NM_001130987.2(DYSF):c.3427del (p.Glu1143fs)

Version: 1.0

CA1139532918

1300184 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: c4e65916-27fa-4cdf-b33c-32a208d91211
Approved on: 2025-06-24
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HGVS expressions

NM_001130987.2:c.3427del
NM_001130987.2(DYSF):c.3427del (p.Glu1143fs)
NC_000002.12:g.71589617del
CM000664.2:g.71589617del
NC_000002.11:g.71816747del
CM000664.1:g.71816747del
NC_000002.10:g.71670255del
NG_008694.1:g.140995del
ENST00000698057.1:c.799del
ENST00000698058.1:c.16del
ENST00000698059.1:c.16del
ENST00000258104.8:c.3373del
ENST00000410020.8:c.3427del
ENST00000258104.7:c.3373del
ENST00000394120.6:c.3376del
ENST00000409366.5:c.3376del
ENST00000409582.7:c.3424del
ENST00000409651.5:c.3469del
ENST00000409744.5:c.3334del
ENST00000409762.5:c.3424del
ENST00000410020.7:c.3427del
ENST00000410041.1:c.3427del
ENST00000413539.6:c.3466del
ENST00000429174.6:c.3373del
ENST00000475076.5:n.201del
ENST00000479049.6:n.258del
ENST00000493767.1:n.94del
NM_001130455.1:c.3376del
NM_001130976.1:c.3331del
NM_001130977.1:c.3331del
NM_001130978.1:c.3373del
NM_001130979.1:c.3466del
NM_001130980.1:c.3424del
NM_001130981.1:c.3424del
NM_001130982.1:c.3469del
NM_001130983.1:c.3376del
NM_001130984.1:c.3334del

NM_001130985.1:c.3427del
NM_001130986.1:c.3334del
NM_001130987.1:c.3427del
NM_003494.3:c.3373del
NM_001130455.2:c.3376del
NM_001130976.2:c.3331del
NM_001130977.2:c.3331del
NM_001130978.2:c.3373del
NM_001130979.2:c.3466del
NM_001130980.2:c.3424del
NM_001130981.2:c.3424del
NM_001130982.2:c.3469del
NM_001130983.2:c.3376del
NM_001130984.2:c.3334del
NM_001130985.2:c.3427del
NM_001130986.2:c.3334del
NM_003494.4:c.3373del

Pathogenic

Met criteria codes 3

PM3 PVS1 PP4_Strong

Not Met criteria codes 1

PM2

Evidence Links 0

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for DYSF Version 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_003494.4: c.3373del p.(Glu1125LysfsTer9) variant in DYSF, which is also known as NM_001130987.2: c.3427del p.(Glu1143LysfsTer9), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 31/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been reported in at least 12 patients with features of LGMD, including in the homozygous state in at least eight individuals (1.0 pt; PMID: 32400077; 26088049; 2324326; 12410383; LOVD DYSF_000024; PM3). It appears to be particularly common among Japanese patients with a Miyoshi myopathy phenotype. At least one of the patients homozygous for this variant displayed absent dysferlin protein expression in skeletal muscle in addition to a clinical diagnosis of LGMD, which is highly specific for DYSF-related LGMD (PMID: 12410383; PP4_Strong). The filtering allele frequency of this variant is 0.00023 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 4/39700 East Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (≤0.0001) (PM2_Supporting not met). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (LGMD VCEP specifications version 1.0.0; 06/24/2025): PVS1, PM3, PP4_Strong.

Met criteria codes

PM3		✔	This variant has been reported in at least 12 patients with LGMD, including in the homozygous state in at least eight individuals (1.0 pt; PMID: 32400077; 26088049; 2324326; 12410383; LOVD DYSF_000024; PM3). It appears to be particularly common among Japanese patients with a Miyoshi myopathy phenotype.
PVS1		✔	The NM_003494.4: c.3373del p.(Glu1125LysfsTer9) variant in DYSF, which is also known as NM_001130987.2: c.3427del p.(Glu1143LysfsTer9), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 31/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PP4_Strong		✔	At least one of the patients homozygous for this variant displayed absent dysferlin protein expression in skeletal muscle in addition to a clinical diagnosis of LGMD, which is highly specific for DYSF-related LGMD (PMID: 12410383; PP4_Strong).

Not Met criteria codes

PM2		✖	The filtering allele frequency of this variant is 0.00023 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 4/39700 East Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (≤0.0001) (PM2, BA1, BS1 not met).

Curation History

Showing 1 to 1 of 1 rows